FLAG Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of Acute Myeloid Leukaemia (AML) in patients unsuitable for treatment with idarubicin or as consolidation post FLAG-Ida	C92	00363a	Hospital
Treatment of patients with high blast count (>10%) Myelodysplastic Syndrome in patients unsuitable for treatment with idarubicin	D46	00363b	Hospital
Salvage regimen for patients with relapsed/refractory acute leukaemia	C91 C92	00363c	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered as described in the treatment table below.
A second cycle may be administered when ANC > 1 x 10^9/L and platelets > 100 x 10^9/L at the discretion of the prescribing Consultant.
Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent and rate
-1 to 6 (7 days)[a] inclusive	[b]G-CSF	5microgram/kg	SC	Round to full syringe
1,2,3,4,5 inclusive	Fludarabine	30mg/m^2	IV infusion	100mls 0.9% NaCl over 30 mins
1,2,3,4,5 inclusive	Cytarabine	[c]2000mg/m^2	IV infusion	500mls 0.9% NaCl over 4 hours. **Commence 4 hours after start of Fludarabine infusion**
[a] G-CSF to be administered for 7 days starting the day before administration of fludarabine and cytarabine (Day -1,1,2,3,4,5,6)				
[b] G-CSF may be continued at the discretion of the prescribing Consultant				
[c]The dose of cytarabine should be reduced to 1000mg/m^2 on Days 1-5 inclusive for patients >60 years of age				

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Age <60 generally. May be used in older patients if deemed fit for intensive therapy by prescribing consultant

EXCLUSIONS:

- Hypersensitivity to fludarabine, cytarabine or any of the excipients
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Haematology Consultant working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Uric acid, LDH, Glucose
- Coagulation profile (Activated Partial Thromboplastin time (APTT), Prothrombin time (PT), fibrinogen level)
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) Hepatitis C, HIV *
  *(**Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation**)

Regular tests:

- FBC, renal and liver profile daily or as clinically indicated
- Uric acid, Glucose daily or as clinically indicated
- Coagulation profile: APTT, PT, fibrinogen level at least twice weekly or more frequently as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- **Renal and Hepatic Impairment:** Dose reduce chemotherapy only after discussion with Consultant

Renal and Hepatic Impairment:

Table 1: Dose modification of Cytarabine and Fludarabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Fludarabine	**Cr Cl (ml/min)**	**Dose**	No dose changes recommended
	>70	100%	
	30-70	50%	
	<30	Contraindicated	
Cytarabine	**CrCl (ml/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.
	>60	100%	
	46-60	60%	
	31-45	50%	
	<30	Contraindicated	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Cytarabine: Moderate **(Refer to local policy)**

Fludarabine: Minimal **(Refer to local policy)**

ANTIEMETICS

Table 2: Recommended antiemetics

Prevention of acute nausea and vomiting			When required for breakthrough emesis	
Drug	**Dose**	**Admin Day**	**Drug**	**Dose**
Ondansetron	8mg three times daily PO/IV	1,2,3,4,5	Cyclizine	50mg three times daily
			Lorazepam	0.5-1mg PO/IV three times daily

PREMEDICATIONS:

To prevent a chemical induced conjunctivitis developing with cytarabine, prednisolone eye drops (e.g. Pred Mild) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered.

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouth/Oral care **(Refer to local policy**
- Severe PV Bleeding **(Refer to local policy)**
- All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation)

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Myelosuppression:** This is a very myelosuppresive regimen**.** Fludarabine and cytarabine are both myelosuppressive agents. Caution is required in pre-treated patients, those with a history of opportunistic infections and the elderly.

Fludarabine:

- **Hepatitis B reactivation:** The immunosuppression associated with fludarabine may increase the risk of re-activation of hepatitis B. If the patient is HBsAg positive consult local hepatologist as per local policy.

Cytarabine:

- **Neurotoxicity:** This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment (Ref Table 1).
- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by fever, flu-like symptoms, skin rash and occasionally chest pain.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Virchis A et al. Fludarabine, cytosine arabinosiode, granulocyte-colony stimulating factor with or without idarubicin in the treatmet of high risk acute leukaemia or myelodysplastic syndromes Br J Haem 2004;124, 26-32
2. Krens S D, Lassche,Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network .
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. Fludara 50 mg powder for solution for injection or infusion. Summary of product characteristics. Last updated Nov 2019. Accessed Nov 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0611-004-001_11112019115658.pdf
7. Cytarabine 100 mg/ml Solution for Injection. Summary of product characteristics. Last updated Sept 2018. Accessed Nov 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_28092018160744.pdf

Version	Date	Amendment	Approved By
1	17/9/2021		NCCP Myeloid Clinical Advisory Group
2	20/12/2021	Updated treatment table	NCCP Myeloid Clinical Advisory Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.